Clinical Proceedings

of the

CHILDREN'S HOSPITAL

WASHINGTON, D. C.

Contents

Vol. III MAY 1947 No. 6

Entered as second class matter November 21, 1946 at the post office at Washington, D. C., under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 538, Act of February 28, 1925, authorized January 17, 1947.

Published monthly by the Children's Hospital, 13th and W Sts., Washington, D. C.

Subscription rate is $1.00 per year.

IDIOPATHIC HYPOGLYCEMIA

Case Report No. 94

Dr. Harrison Spencer J. L. 46–11894

J. L., a 21 month old white male, was brought to the Naval Dispensary on the morning of December 25, 1946 with the chief complaint of "unconsciousness." History obtained at this time revealed that the infant had been well until 2 days preceding, when he had received a routine injection of .5 cc. typhoid vaccine. No reactions or untoward symptoms were observed by the parents for the next 24 hours. Then, one day before admission, the child appeared irritable and fussy with a poor appetite, but no apparent fever. He slept well that night but awakened the day of admission with a desire but inability to walk. According to the mother "he seemed to stumble and fall." Subsequently, he became sleepy, refused all food and fluids, and became quite irritable. Shortly thereafter the infant screamed, threw his head back and forth, drew his legs up, vomited and then fell into a state of wide-eyed staring coma.

There was no previous history of convulsions nor family manifestations of neurological or epileptic disorders. The infant's birth, neonatal and developmental history were not remarkable.

The infant was immediately admitted to Children's Hospital. There on admission physical examination, the following positive findings were recorded: T—98°, Pulse—110, Respirations—20. The child was described as a well-developed, well-nourished 21 month old white male who appeared acutely ill. He lay quietly in bed, staring into space, responding only to painful stimulation and moaned continuously. The pupils reacted to light. The breath had an acetone odor. Neurological examination revealed only the clouded sensorium, ataxic-like movements and semi-comatose state with no pathological reflexes. An intravenous injection of 250 cc. of 5% glucose with Hartmann's solution was given. Following this there was a most dramatic change in the patient's condition. The wide-eyed staring, comatose state disappeared and the child became interested in his surroundings, walked with help and responded readily to simple commands. The next morning a fasting blood sugar was 47 mgm. % and urinalysis showed 2 plus sugar and 3 plus acetone. The urinary findings were thought to be due to inanition, vomiting and intravenous glucose. The child's condition seemed good and so he was discharged on the second hospital day to be followed in the Naval Dispensary.

The patient was not seen again until the morning of January 31, 1947, when he was brought to the Naval Dispensary with a complaint of "con-

vulsions" which started two hours before. The convulsion was a generalized clonic seizure. The child had a wild, staring gaze with loss of sensorium, widely dilated pupils which did not react to light, and a very low threshold of irritability. Chvostek and Trousseau signs were negative and neurological examination was again not revealing. Temperature was 99.2° (R). A venous blood sugar and calcium level were obtained following which the child was given 5 cc. calcium gluconate and 10 cc. of 50% glucose intravenously and a suppository of grains one and a half seconal was inserted rectally. Within about 10–15 minutes a rather striking improvement was noted. The sensorium cleared, the child became responsive to his surroundings and the convulsion ceased.

X-ray examination of the skull taken at the Naval Dispensary prior to hospitalization was negative. The blood sugar was reported to be 25 mgm. %. The calcium level unfortunately was lost through a laboratory error.

The child was then admitted to Children's Hospital for observation. The physical examination at the hospital was not revealing. A spinal tap performed at the time of entry was negative.

Following this procedure an intravenous of 100 cc. 5% glucose in saline was given. A fasting blood sugar the next morning was 28 mgm. % but no further convulsive seizures occurred and the child was asymptomatic for the remaining seven-day stay in the hospital. He was placed on a high protein, high carbohydrate and low fat diet with supplementary nourishment in between meals and at 9 P.M.

During this hospital admission several laboratory procedures were carried out directed toward determining the etiology of this afebrile convulsive seizure. Fasting blood sugar taken on the morning of the second hospital day was 28 mgm. %. With improvement in the patient's appetite, a fasting blood sugar on the third day was 67 mgm. % with an NPN of 33 mgm. %. Total protein was 4.5 mgm. %; and one week later was 5.5 mgm. %. Oral and intravenous glucose tolerance tests were done and were normal. Cephalin flocculation was negative in 48 hours. Urinalyses were not abnormal. The child's mother and father's fasting blood sugar levels were 86 and 88 mgm. % respectively.

The patient was discharged on the eighth hospital day doing nicely on the above diet with supplementary nourishments. Since his discharge, the child has been followed in the Naval Dispensary. He is doing quite well with no recurrence of convulsive seizures.

DISCUSSION

Dr. Harrison Spencer: Here we have presented a case of convulsions and syncope associated with a low blood sugar in a previously normal, healthy

21 month old child. Clinically the striking features were the occurence of attacks early in the morning, low body temperature, evidence of ketosis, poor fluid intake, vomiting, convulsions and comatose state. The rapid return of sensorium with the intravenous injection of glucose solution was one of the first diagnostic clues in this case. The blood sugar values of 47 mgm. % and 25 mgm. % then made rather certain the classification of this case as one of recurrent severe hypoglycemia. Efforts were then directed toward determining the etiological basis of the spontaneous hypoglycemia. Glucose tolerance tests using 2.0 gms. of glucose per pound of body weight by oral and intravenous routes were performed. The results of these were interpreted as normal curves and showed that the absorption of glucose from the gastrointestinal tract was not at fault and that the glucose was rapidly mobilized from the blood stream. Frequent negative urinalyses did not bear out the possibility that the hypoglycemia could be on a basis of renal glycosuria. The history of this infant did not reveal undue and excessive carbohydrate intake with sudden removal prior to the attacks of hypoglycemia, as suggested by Hartmann and Jaudon as a cause of physiological hyperactivity of the Islands of Langehans leading to true hyperinsulinism and ensuing hypoglycemia. Liver abnormalities were considered as a cause of the hypoglycemia. However the child's liver was not enlarged nor tender; there was no jaundice, acholic stools, nor obvious prothrombin deficiency and the cephalin flocculation test was negative in 24 and 48 hours.

The possibility of a pancreatic tumor was considered unlikely on a statistical basis, there having been reported only one authenic pancreatic tumor causing hypoglycemia in a child in the literature up to 1937. This was the case of Wolf et al in 1933.

We were then left with the possibility that the hypoglycemia was caused by lack of development or breakdown of the regulatory mechanism leading to relative hyperinsulinism. This might well be explained on an endocrine inbalance i.e. adrenal or pituitary insufficiency. That such is the best explanation for the hypoglycemia in this case is substantiated by the results of the insulin tolerance test. Here $\frac{1}{4}$ unit of crystallin insulin per kilo body weight (3 units total) was given subcutaneously ten minutes after 2 gms. of glucose per pound was given orally. Blood sugars, using micro-capillary whole blood technique, were then taken for the glucose tolerance tests with the following curve obtained:

Fasting	63
½ hour	83
1 hour	59
2 hours	37
3 hours	42

This curve, we feel, showed a rather abnormal effect of the small dose of insulin and compares quite favorably to the curves obtained by Hartmann in his children with hypoglycemia whom he classified in this group. They too showed an insulin intolerance with prolonged lowering of the blood sugar. Hartmann considers this an important diagnostic criterion. The insulin effect, he explains, is most probably due to lack of storage of liver glycogen and/or lack of proper opposition to insulin activity by epinephrine or anterior pituitary hormone by causing mobilization of liver glycogen. He remarks that these patients show decreased food intake, food loss from vomiting and unusual energy expenditure prior to attacks. Hartmann and Jaudon present one case where there seemed to be some familial tendency. We could obtain no such familial evidence in this case.

We were very desirous of obtaining an adrenalin tolerance test on this infant but were unable to do so since the family subsequently moved away from Washington.

GENERAL DISCUSSION

*De Lora Fowler:** The blood sugar is kept at normal levels by certain control mechanisms which operate not only in hypoglycemic emergencies but at all times. Ingested carbohydrate, amino acids of protein and the glycerol fraction of fat are sources of blood glucose. The liver stores carbohydrate and is also the chief site for the conversion of glycerol, amino acids, lactic and pyruvic acids to glycogen which is released into the blood between meals. Thus, glucose continuously arises in the normal person by absorption from the gastro-intestinal tract and by synthesis. In general, before glucose can be utilized by the body it must be phosphorylated—a reaction catalyzed by the enzyme hexokinase.

$$\text{glucose} + \text{adenosine triphosphate} \xrightarrow{\text{hexokinase}} \text{glucoe-6-phosphate} + \text{adenosine diphosphate}$$

Once formed, glucose-6-phosphate may (a) be regenerated to glucose by the liver phosphatase (b) be made into glycogen (c) form carbon dioxide and water (d) be converted into fatty acid. All of these substances are formed in normal amounts if the hexokinase reaction is proceeding at a normal rate. If this reaction is accelerated, glucose is burned too rapidly and unless carbohydrate is continuously supplied, hypoglycemia will follow. Excess of insulin, lack of anterior pituitary inhibitor or lack of certain adreno-cortical steroids will increase hexokinase activity and, therefore, increase the rate of glucose oxidation. If, on the other hand, the hexokinase reaction is inhibited, there is a slowing down in the rate of glucose utiliza-

* Miss Fowler is a senior medical student at George Washington Univ.

tion with consequent hyperglycemia. This is probably what occurs in the diabetic person.

Factors increasing blood sugar: The role of adrenalin in carbohydrate metabolism is of two types. In the well nourished animal, low blood sugar levels stimulate centers in the hypothalamus, medulla oblongata and pons which send impulses along the splanchnic nerves to the adrenal medulla. Adrenalin is released and mobilizes liver glycogen so that blood glucose increases. Section of the splanchnic nerves almost completely prevents this response. In the previously fasted animal, where liver glycogen is already depleted, adrenalin produces a decrease in muscle glycogen, a rise in blood lactate, and a secondary rise in liver glycogen. Under these circumstances, the liver uses a portion of the lactate formed in muscles for glycogenesis. Thyroid and posterior pituitary act synergistically with the adrenal medulla.

Recently, the Coris have shown that the phosphorylation of glucose—a reaction required before glucose can be utilized by the body—is inhibited by a substance obtained from the anterior lobe of the pituitary. This inhibiting effect of the anterior pituitary is prolonged by the adreno-cortical steroids but overcome by insulin. When the anterior pituitary and adrenal cortex become excessive, there occurs a diabetes which is part of the syndrome of acromegaly.

Anterior pituitary and adrenal cortex also work against low blood sugar levels by repressing the oxidation of carbohydrate and, therefore, are diabetogenic. Some investigators believe that the more oxygenated adreno-cortical steroids aid in the conversion of glucogenic amino acids into glucose. The evidence on which this is based (increase in blood sugar, liver glycogen and urinary nitrogen after adreno-cortical steroids are given) is very suggestive but as yet the mechanism of action is not clear. The low blood sugar seen in hypoadrenalism is perhaps aggravated by this interference with gluconeogenesis. Through stimulation by the anterior pituitary and adrenal cortex, the internal secretion of the ovary is also diabetogenic.

Factors decreasing blood sugar: Hyperglycemia stimulates parasympathetic centers in the hypothalamus and medulla oblongata which through the vagus nerves apparently cause an increase in insulin by stimulating the Islets of Langerhans. However, the islets also react directly to an increase in blood sugar if the pancreas is denervated. Possibly the nervous reflex is of minor importance and simply increases the sensitivity of the islets.

Hypothalamic lesions have been shown by Keller to produce hypoglycemic crises.

Pathology: In chronic hypoglycemia of severe degree there is usually central nervous system damage, the changes resembling those seen in anoxia. The cerebral cortex and basal ganglia show edema, chromatolysis

and perivascular hemorrhage which at first are reversible. Later there is death of the nerve cells with replacement by astrocytes, and loss of myelin. This damage is permanent and probably due to failure of oxidation from a lack of glucose substrate and worsened by the subsequent vasomotor disturbance.

The brain of the fetus and newborn is less susceptible to permanent damage by anoxia. It is suggested that the tolerance of young dogs to anoxia and hypoglycemia is related to a low cerebral metabolic rate and to an anaerobic source of energy.

Classification—A. True Hyperinsulinism: In infants of diabetic mothers, a period of hypoglycemia occurs 2 to 24 hours after birth, and most cases are probably due to an increased physiologic hyperactivity of the islets as a result of a high sugar level in the mother. Physiologic hyperactivity, or the Staub-Traugott phenomenon, where frequent ingestion of carbohydrate may result in a decided hypoglycemia is most often seen between the age of one year and the age when the child is able to regulate his own food intake. Waddell reports the case of a two year old who frequently made secret raids on the family ice-box. Convulsions and unconsciousness were the clinical manifestations of hypoglycemia when the ice-box was padlocked.

Of course, the most common cause of low blood sugar is insulin administration. Islet tumors are rare in childhood.

B. Relative Hyperinsulinism: Paucity of glycogen storage, particularly in the liver, or insufficient absorption of carbohydrate from the intestinal tract will precipitate hypoglycemia. Malnutrition developing from feeding problems, weaning or failure to ingest sufficient food causes diminished intestinal absorption. Disease of the small bowel such as diarrhea, vomiting, fistula, pyloric stenosis, with or without superimposed infection, produces a combination of decreased intake and increased utilization. In myxedema and sprue, the failure of the blood sugar to increase after oral glucose has been attributed to faulty absorption by the intestinal mucosa.

The central position of the liver in maintaining a constant blood sugar level should be stressed. Disease of this organ may bring about hypoglycemia by damaging the glycogenolytic or glycogenic functions or by damaging storage capacity. Although only 20% of normal liver tissue is necessary to maintain adequate resting carbohydrate metabolism, sufficient liver destruction is seen in salicylate poisoning, acute catarrhal jaundice, liver poisons and severe infections (diphtheria) so that hypoglycemia results. In von Gierke's disease, there is abundant glycogen stored in the liver but it fails to serve as a source of glucose. Here it may be suspected that one of the systems which is deficient is the liver phosphatase.

Lack of development of the regulatory mechanism in normal newborn infants results in a mild hypoglycemia during the first four or five days of

life and in them seems to be due to a state of relative hyperinsulinism. As his neuro-endocrine balance is not stabilized, the infant is at a greater disadvantage than the adult when carbohydrate supplies to the liver are reduced.

Endocrine imbalance is a very important factor. Hemorrhage into the adrenals is not rare in newborns. This produces decreased epinephrin in the blood and deficient liver glycogenolysis ensues. Some children tend to have recurrent attacks of very severe hypoglycemia which probably are due to the lack of insulin antagonists. Failure of nay one of the endocrines regulating the blood sugar level does not lead to a fatal attack as there is reduplication of action which prevents grave hypoglycemia in hypothyroidism or destruction of the posterior pituitary. When, however, the cortex of both adrenals is destroyed as sometimes in Addisons Disease, there is a more severe hypoglycemia because not only is a diabetogenic hormone lost but also a hormone accelerating the formation of carbohydrate from protein. The entire endocrine defense rests on the anterior pituitary. Therefore, in Simmonds disease, there is a grave hypoglycemia as the thyroid and adrenal cortex suffer secondary degeneration.

Severe hemorrhage into the base of the brain is said to produce hypoglycemia. Hypothalamic lesions cause crises which cannot be prevented either by vagotomy or sympathectomy.

A number of cases of hypoglycemia are due to an autonomic imbalance or "functional hyperinsulinism". These cases are characterized by a normal fasting blood sugar with a tendency for the level of the blood sugar to fall abnormally low from three to five hours after the ingestion of carbohydrate. The tired people with mental and physical inertia due to hypoglycemia probably fall in this category.

C. Cryptogenic: Holt says that this is the most important and most troublesome type of hypoglycemia. Rector and Jennings from a study of eleven cases, consider that the rare occurence in children of hypoglycemia with recurrent convulsive manifestions is usually found between the ages of one and three years and is due to a functional hepatic disorder of an intermittent nature. The exciting cause is a temporary depletion of glycogen reserve usually due to insufficient food intake. It is also possible that the pituitary or adrenal cortex are at fault.

Signs and Symptoms: "Glucose is the main source of energy for the central nervous system. Since a fire may be extinguished equally well by removing the combustible material or by excluding oxygen, it is not surprising that the signs and symptoms and results of hypoglycemia and anoxemia are almost identical. This similarity is also striking in the pathological changes found in the brain of patients subject to recurring attacks of marked hypoglycemia" (Aranow).

The most prominent symptoms of hypoglycemia are those involving the central nervous system. They appear first, remain throughout the episode and are the most dangerous. Studies indicate that profound hypoglycemia may depress cerebral metabolism to one fourth the normal rate.

In the older child where cerebral function is already well integrated, signs of hypoglycemia may be divided into five phases. The first of these begins when the blood sugar begins to fall away from its normal level and continues until the lowest point is reached. The remaining four phases follow successively as long as the low level persists. The sequence of the signs and symptoms is always unaltered, and may be explained on the basis of the metabolic rate of the various regions of the brain. Because they metabolize at the highest rate, the cerebral hemispheres and parts of the cerebellum are the first to react to a low blood sugar. The medulla oblongata, being the oldest part of the brain continues to function long after the other regions of the brain are unable to do so.

(1) Cortical phase. Within the first half hour, there is somnolence, mental retardation, clouding of consciousness and failure in orientation; at times there is wild excitement. Associated with this is sweating, salivation, flushing or pallor, and tremor.

(2) Subcortico-diencephalic phase. When the motor nuclei in this region are freed from cortical suppression, primitive movements as sucking and grasping are seen. There is great restlessness and muscle twitching may be vigorous and generalized. Stimulation of any part of the body produces a reaction like that to a painful stimulus.

(3) In the third or midbrain stage, tonic spasms predominate. The arms are flexed and the legs extended. Torsion spasm, where the body twists about its own long axis, may occur. The eyes move independently of each other.

(4) Upper part of the Medulla oblongata. Here the body and legs are arched and the arms extended. This phase resembles closely the picture of the decerebrate dog of Sherrington where the brain is sectioned through the mesencephalon.

(5) Lower part of the medulla oblongata. The vital respiratory and cardio-vascular centers are located here, and obviously the patient is in serious danger when this part of the brain is involved. Coma is deep and parasympathetic signs predominate as indicated by the shallow respiration, slow heart rate, bloodless skin, pin-point pupils which do not react to light. The body temperature is low, the muscles relaxed and the tendon jerks depressed. If glucose is administered during the first fifteen minutes of the last phase, the signs proceed in the reverse order of development and the patient recovers quickly. If treatment is delayed, recovery is retarded and may be accompanied by persistent neurological signs.

The attack may arrest at any stage, spontaneously or with glucose. In the mildest form complaints are vague: weakness and disinclination for physical and mental exertion. A number of patients with hyperinsulinism are referred to the neurologist with the diagnosis of hysteria, sometimes because of character and personality changes, some vague psychosis, mild dyskinesia or convulsion. There may be headaches of the migrainous type.

Hypoglycemia may well be regarded with anxiety as its harmful effects on behavior are both immediate and delayed. Young children become irritable and fretful and failure to understand the cause of the child's erratic conduct often starts a chain of circumstances which affect his future behavior. Often these children are scolded or punished because of actions beyond their control. Sometimes children and adolescents may exhibit confusion, negativism and violent outbursts. One often finds erratic behavior at school.

Diagnosis: The diagnosis of hypoglycemia is a matter of having the condition in mind when there are episodes of cerebral dysfunction, and of making blood sugar determinations at this time. It should be remembered that the absolute value of the blood sugar may not have as much significance in the individual patient as its value in relation to his usual levels, and the rate with which it falls.

Once the diagnosis is made there are a number of procedures which can be used to determine the cause.

(a) Glucose Tolerence Test. After the ingestion of glucose, the patient may show a flat curve where poor intestinal absorption is a factor.

A biphasic curve is thought to be caused either by a too rapid uptake of the sugar from the intestine by the liver or by an unusual output of insulin. This is the functional type of hypoglycemia and signs and symptoms appear in three to five hours when the blood sugar is abnormally low.

Organic hypoglycemia, on the other hand, appears after fasting. Aranow believes that Whipple's triad indicates a search to organic pathology such as pancreatic tumors:

1. Repeated attacks in the fasting state.
2. Blood sugar below 50 mgm. % during an attack or after a prolonged fast.
3. In the earlier stages, relief of an acute episode by glucose.

A low fasting value followed by a Janney diabetic curve after glucose is found in hyperinsulinism.

(2) Insulin sensitivity is said by some investigators to occur only in those cases of hypoglycemia due to lack of insulin antagonists. Holt, however, thinks that is is found in all types of hypoglycemia and, therefore, is not diagnostic.

(3) Epinephrin tolerance test in which the blood sugar is followed after

injection of ½ m. 1:1000 solution per kilo of body weight will show to what extent the liver is able to perform its glycogenolytic function.

(4) Carbohydrate withdrawal test. This is a test of glycogenic function and is a guide to the usefulness of a high protein diet in treatment. If carbohydrate is omitted and the patient fed adequate calories derived from fat and protein, certain patients are able to form sufficient sugar from these and will maintain their blood sugar levels. Other patients are unable to do so and develop hypoglycemia in 24 hours or less.

(5) The respiratory quotient indicates what the tissues are burning. When hypoglycemic patients are fasted, they can be separated into two groups by the behavior of the R.Q. As the blood sugar falls, some will respond by burning less carbohydrate and more fat. Others will continue to burn carbohydrate without any diminution in its combustion. The last group presents a very serious therapeutic problem for which surgery may be the only answer.

All of the tests have on serious shortcoming. One cannot differentiate between hyperinsulinism and lack of insulin antagonists.

Wechsler and Garlock believe that the EEG is a very important addition in the diagnosis of hypoglycemia. The disturbance in brain rhythm is typical for the hypoglycemic state with or without shock. An EEG tracing of an epileptic nature which promptly returns to normal after glucose is given (a temporary return) and permanently returns to normal after the successful removal of a pancreatic adenoma is a diagnostic criterion and also a test of the success of the operation.

Therapy: Infants of diabetic mothers should be watched very carefully for the first four or five days of life. They should be started on feedings of milk and sugar water between feedings quite early. Epinephrin or glucose is given parenterally for a hypoglycemic emergency.

If it is thought that the child has hyperinsulinism due to a pancreatic adenoma, resection of the pancreas is indicated because of the danger of ultimate malignancy. Dietary regimes for these cases are only palliative.

The aim of therapy in chronic functional hypoglycemia is to supply a steady, slowly available dietary source of glucose. High protein diets which produce continuous gluconeogenesis result in a less marked post-prandial rise and fall in blood sugar. The Mayo Clinic uses a normal diet except that the protein is increased to 2 gms. per kilogram of body weight per day.

REFERENCES

Brennemann: Practice of Pediatrics, Vol. 1, Chap. 24.
Hartmann, A. F., and Jaudon, Joseph C.: Journal of Pediatrics, **15:** 1937.
Conn, J. W., and Newburgh, L. H.: Journal of Pediatrics, **15:** 665, 1936.

Wolf, A., Hare, C., and Riggs, A.: Bull. Neur. Inst. N. Y., **3:** 232, 1933.
Anderson: Lancet, London, **2:** 1940.
Aranow, H.: Am. J. Med., **1:** No. 4, Oct. 1946.
Aub, Nathanson and Town: Arch. Neur. Psychiat. Chic., **45:** 1941.
Gammon: In. Pract. Libr. M. and S., 1938 supplement.
Best and Taylor: Physiological Basis of Medical Practice, 3rd Ed.
Hartmann and Jaudon: J. Peds., **11:** 1, 1937.
Harris, S.: J. A. M. S., Dec. 16, 1933.
Harris: Ann. Int. Med., **7:** 1084, 1934.
Himwich, H. E.: Am. J. Digest. Dis., **11:** 1944.
Holt, L. E., Jr., and Bridge, E. M.: Nebraska J. J., **30:** 1945.
Cameron, A. T.: Recent Advances in Endocrinology. Blakiston Co., 1945.
Fischer, A. E., and Dolger, H.: Arch. Int. Med., **78:** Dec. 1946.
Long, Katzen, and Fry: Endocrinology, **26:** 309, 1940.
Neale, A. V.: Proc. of Royal Soc. of Med., **39:** No. 11, 1946.
Prunty, F.: British Med. J., **2:** 1944.
Sevringhaus: Endocr. Ther., 3rd Ed., 1940.
Turner: Bull. Chicago M. Soc., **49:** 1946–47.
Waddell, W. W., and Humphries, T. J.: Virginia Med. Monthly, **68:** 1941.
Wagner: N. England J. M., **229:** 1943.
Wechsler, I. S., and Garlock, J. H.: Journal of Mt. Sinai Hosp., **10:** 1943–44.
Yannet: J. Peds, **24:** 1944.
Stetten, D.: J. A. M. A., **132:** No. 7, Oct. 1946.

CONGENITAL ANOMALIES OF THE BILE DUCTS

Mark Moots:*

Congenital anomalies of the extrahepatic biliary system are not infrequently encountered in pediatric practice. Approximately 200 cases of agenesis or atresia of the bile ducts and/or gall bladder were reported up to 1936, and in the past decade numerous reports of similar anomalies have more than doubled that figure. This report represents a study of thirteen cases seen at The Children's Hospital in the past four years and includes a review of the literature on this subject. Two of the cases have been reported previously by Stiegler and Warfield in the Clinical Proceedings of Children's Hospital.[1]

NORMAL EMBRYOLOGY

When the embryo is but four weeks old (2.5 mm.), an evagination called the hepatic diverticulum arises from the duodenal portion of the foregut. Its cephalic portion is solid and is destined to form the liver, while the caudad portion is hollow, continuous with the lumen of the gut, and is destined to become the extrahepatic biliary system. Constriction of the entire diverticulum occurs, so that the pars hepatica, while generating into liver lobules, is connected with the intestine through but a narrow cord of cells. It is generally believed that epithelial proliferation accounts for the loss of patency in these ducts, and that later these solid cords recanalize.[2]

The liver parenchyma develops rapidly and the whole organ is comparatively huge at nine weeks, lobes being recognizable early. With the completion of the recanalization process of the pars cystica, the formation of the intra- and extrahepatic systems is finished, and secretion and passage of bile occurs during the twelfth embryonic week.[3]

PATHOLOGIC EMBRYOLOGY

The exact etiology of agenesis and atresia of the bile ducts is unknown. Simple failure of the hepatic diverticulum to form, and if it does form, simple failure of recanalization of the pars cystica, is, of course, the most attractive theory of the etiology of agenesis and of atresia respectively.

But why should this ever happen? Moolten[4] states that there are two factors concerned in cell differentiation in embryonic life, namely "cell-competence" (the intrinsic predisposition of the primitive cell to specialize) and "organizer-induction" (specialized cells which liberate a chemical stimulus for growth of other cells). He feels that atresia offers a clearcut example of defect in cell-competence, because the anomaly is one of de-

* Mr. Moots is a senior medical student at Georgetown Univ.

velopmental failure, and lacks features of overgrowth, a dysfunction of "organizers". Segmental atresia is the end result of limited suppression.

Local suppression may also be represented by agenesis of the gall bladder with or without atresia of the ducts. Agenesis of the gall bladder may be explained in two ways, namely, failure of the organ to develop as an outpocketing of the hepatic diverticulum, or arrest in the obliterated stage.[5] Its absence without congenital obstruction in the ducts rarely occurs in humans, and does not impair health or digestive function.

Nutting and Wells[2] in 1945 reviewed the literature on the etiology of duct anomalies, and in addition to the attractive theory of Moolten presented the following for consideration: (1) catarrhal inflammatory processes in the liver, descending into the bile ducts and causing their complete occlusion; (2), absorption of toxins from the mother which injure the liver and bile ducts of the fetus; (3), syphilis; (4), mechanical traction of the mesentery, twisting the ducts; (5), fetal peritonitis with adhesions and constriction of the ducts; and (6), abnormalities in vascular supply resulting in deformity of the duct.

PATHOLOGIC ANATOMY

While it is obvious that the locus of obstruction in the duct system in any one case may not be identical to those of scores of other such lesions, nevertheless it behooves us to classify the malformation into one of several small groups. Ladd's[6] classification leaves little to be desired, and is as follows:

Group I. Cases in which there are no extrahepatic ducts.

Group II. Cases in which there is an atresia of the hepatic ducts.

Group III. Cases in which there is an atresia of the common bile duct.

Group IV. Cases in which the gall bladder is represented by a moderately sized cyst not connected to the common bile duct and in which there may or may not be any common or hepatic ducts.

Group V. Cases in which the gall bladder connects directly with the duodenum but in which there are no other hepatic ducts. That is, no ducts connect the liver and gall bladder or the liver and intestine.

Group VI. Cases in which there is a stenosis of the common duct plugged with inspissated bile causing complete obstruction.

Group VII. Cases in which there is a narrowing of the common bile duct causing portal obstruction.

Closely associated with and secondary to obstruction of the duct system is biliary cirrhosis of the liver. So commonly is it seen that Nutting and Wells advise liver biopsy in cases of undiagnosed neonatal jaundice to establish the diagnosis.[2] Grossly and histologically, the liver is likened to that of pure portal cirrhosis, except that the bile canaliculi and biliary passages are loaded with bile pigment. The fibrous tissue radiates from the bile ducts, and not only surrounds but invades the liver lobule.[7]

PATHOLOGIC PHYSIOLOGY

There are two main effects produced by complete extra-hepatic blockage of bile, from which spring a multitude of interesting phenomena. These two effects are: (1), obstructive jaundice, with subsequent biliary cirrhosis, and (2), lack of normal digestion and absorption of fat and fat-soluble vitamins in the intestinal tract.

The characteristics of obstructive jaundice are well known. Jaundice itself is due principally to suppression of secretion of bile in the liver, and not due to the regurgitation into the blood stream of bile already secreted. For secretion continues only until the pressure in the ducts equalizes the secretory pressure of the liver cells. Once that has occurred, bile passes from the blood into the liver cell, but cannot be secreted, and hence is absorbed into the blood stream and lymphatics.[8]

In obstructive jaundice, the hyperbilirubinemia tends to be pronounced with deep staining of the sclerae and skin, a remarkable yellowish green color. The icterus index usually ranges between 50 and 200 units, and the qualitative van den Bergh is direct and immediate. There is an absence of bile in the stool at all times, except in the rare instance when bile may be carried by the blood to the intestinal mucosa, and be secreted from the mucosa into the bowel lumen.[6] There is a highly positive test for bile in the urine, but no urobilinogen is present in stool or urine.

Bradycardia, which is a common manifestation of obstructive jaundice, is thought to be due to the action of bile salts. Leucopenia and pruritus remain unexplained as yet, although leucopenia may be due to slight splenic enlargement.

In the liver, the process of cirrhosis is constantly going on, and as a result of blockage of the portal venous flow, ascites may develop in the later stages of the course. Low total protein and especially low serum albumin contribute to the production of ascites and subcutaneous edema.

Bile is essential for the efficient digestion and absorption of fat by pancreatic and intestinal juices. While cleavage of the fat molecule may be accomplished with the aid of gastric lipase in the absence of bile, the transportation of the split molecule across the intestinal mucosa is greatly interfered with. Thus 75–85% of ingested fat is found in the stools of these patients.

The most marked effect on vitamin absorption is seen in regard to Vitamin K. Bleeding tendencies are frequently encountered. They are usually characterized by a prolonged prothrombin time, normal coagulation and bleeding times, and a normal thrombocyte count.[9, 10] Poor liver function and mild splenomegaly may contribute to the production of this phenomenum. Also, Naffziger et al[11] report that coagulation defects may result from retention of certain sulfur compounds which are anticoagulants.

Moderate anemia, most often microcytic hypochromic, is usually seen in these infants, and is the result of a combination of poor absorption from the intestinal tract, diffuse liver cell injury, mild splenomegaly, and bleeding tendencies.

SYMPTOMS AND SIGNS

Jaundice is the cardinal symptom. It may be evident at the time of delivery, but more commonly manifests itself between the fourth and tenth days of life. However, one of our patients did not become jaundiced until the fifth week of life. The jaundice usually intensifies for two to three weeks, after which time it remains the same depth. The range of icterus indices, which we considered better indications of the depth of jaundice than the quantitative van den Bergh test, was 25 units to 279 units in our series, with an average of 87 units. These tests were run generally the day after admission.

The usual history given by the parent was one increasing jaundice, chalkiness of the stools, and passage of dark urine. Hypersensitivity of the skin was not noted in any of our cases, although it has been reported.[2] Sweet reports a case with clubbing of the fingers, but we had none in our series.[12]

Gastrointestinal upsets were frequently encountered, vomiting, diarrhea, and constipation being the most frequent symptoms. Constipation and diarrhea were observed with equal frequency. Failure to gain weight was the chief complaint in one case.

Bleeding tendencies were seen on five occasions. These varied from petechiae and ecchymoses on the body surface to the finding of occult blood in the stook, otherwise unexplained. Epistaxis and bleeding gums have been reported,[13] but it was not encountered in our series. Laboratory investigation led to the conclusion that the prothrombin must be lowered to 40–50% of its normal value before such a tendency asserts itself. Infants with prothrombin times approaching even 65% of normalcy did not show evidence of hemorrhagic diathesis. Prothrombin deficiency in one case which died after exploratory laparotomy had shown complete agenesis was evidenced by absence of clotting in blood post mortem, pulmonary hemorrhage, and extensive intracerebral hemorrhage. Bleeding times, coagulation times, and thrombocyte counts were within normal limits in all our patients.

Generally, the physical findings on examination were those of a deeply icteric infant, with moderate hepatic enlargement of two to four finger breadths below the right costal margin, and mild splenomegaly. In one case in which the anomaly was cystic in nature, palpation also revealed a large, cystic, orange-sized mass, filling the right side of the abdomen. Distention of the abdomen due to fluid was noted in six cases. In one

other case the abdomen was distended but tympanitic, the result of fluid and gas in a hypotonic bowel. Venous patterns on the anterior abdominal wall were described on two occasions.

Rickets was prominent feature in one case, that of a five month old female infant. Craniotabes and Harrison's grooves were found on examination, and roentgenographic study revealed typical bone lesions.

DIFFERENTIAL DIAGNOSIS

The necessity of differentiating medical from surgical jaundice needs no comment. Most of the jaundices of infancy are hemolytic in nature, but qualitative van den Bergh reactions, and tests for bile in the stool do not always furnish one with a clearcut diagnosis. Furthermore, there is no reason why one infant cannot have two etiologic factors in the production of its jaundice, although this is undoubtedly uncommon.

Physiologic icterus of the newborn accounts for 98% of all neonatal jaundice.[14] It begins 24 to 72 hours after birth, deepens to a reddish color for a few days, and then fades to disappear in two weeks. Stools are normal while the urine may contain bile. The liver and spleen are not enlarged. The van den Bergh is usually indirect, and the icterus index only slightly elevated.

Erythroblastosis foetalis is a common cause of jaundice at this age. Here the jaundice usually begins 24 to 48 hours after birth, but in the more severe cases the infant is born jaundiced, and the amniotic fluid tinted yellow. Liver and spleen are usually enlarged. Diagnosis is made from the obstetrical history, the clinical picture, and the demonstration of proper Rh agglutinogen setup in parents and infant.

Septicemia usually occurs after the fourth day of life. The skin is usually yellow, and often dotted with petechiae. The infant may suffer a gross hemorrhage. Liver and spleen are not uncommonly enlarged. Laboratory examinations of blood, urine, and stool indicate a hemolytic jaundice, and frequently blood culture is positive.

The other conditions producing jaundice in the newborn are less common and include Winckel's disease, congenital syphilis, and congenital heart disease. Winckel's disease is the rare triad of cyanosis, jaundice, and hemoglobinuria.[14] Congenital syphilis is diagnosed by the presence of varied luetic stigmata, x-ray examination of the long bones, and maternal and infant serology. The diagnosis of congenital heart disease rests with cardiac examination, and the finding of signs corroborative of the anomaly.

While the above may be excluded by careful history, physical examination, and laboratory workup, the differential diagnosis between anatomic obstruction of the bile ducts or that due to inspissated bile or mucous is not so easy. When the case is gotten early, daily stool examinations for

bile may offer the solution to the problem, but more often the final answer is known only after surgical exploration.[15]

TREATMENT

Once the diagnosis has been made, exploratory operation is the next step. The aim of the surgeon is to start bile flowing into the intestinal tract and to keep it flowing. 100% mortality can be expected if the obstruction is not relieved, except in those cases in which there is a spontaneous passage of inspissated material through an otherwise patent system.

It is better not to operate before the end of the first month.[6] Nothing is lost by this delay, and it affords time to assure the correctness of the diagnosis, and to build the patient up as best one can. The usual preoperative regime which we followed consists of the following: (1) normal feedings or lactic acid formula; (2) 5% glucose in 75–100 cc. of physiologic saline via hypodermoclysis twice a day; (3) blood and/or plasma, 8–10 cc. per pound of body weight as indicated; (4) Hykinone, Vitamin K, one ampule (3.2 mgm.) intramuscularly twice a day; (5) Ascorbic acid, 25 mgm., intramuscularly twice a day; (6) Drisdol, 5 drops twice a day, and (7) various diagnostic laboratory procedures, including x-ray of the long bones.

It is not wise to wait longer than six weeks before operating. These jaundiced infants are then past the peak of preoperative buildup, are often in protein deficit despite therapy, and are highly susceptible to respiratory and urinary tract infection.

The type of operative procedure one does depends, of course, upon what part, if not all, of the duct system is atretic. Thompson[16] and Holmes[17] first described the surgical techniques in these cases, and later Ladd described his procedure.[6] If there is agenesis or complete atresia the situation is inoperable. Atresia of the lower portion of the ducts, i.e., the part of the common bile duct nearest the duodenum, seems most amenable to surgery, and one has the choice of anastomosing the gall bladder to the stomach or the duodenum. Before anastomosing the gall bladder to the stomach or intestine, one should have good evidence of the patency of the ducts between the gall bladder and the liver, and, as was our custom here, the system should be inspected by saline injection. The usual technique employed by Ladd[6] is an end to side anastomosis over a small piece of rubber tube using a single row of uninterrupted mattress sutures of fine silk. The rubber catheter is left in place to be carried out by intestinal peristalsis.

In one of our cases the gall bladder was small and contained no bile, but beside it was an opening in the duct system which was draining bile into the peritoneal cavity. This was brought down and anastomosed to the stomach, and the patient is still living, now 2½ years old.

PROGNOSIS

It is apparent that the prognosis depends upon the type and location congenital anomaly that one has, for prolonged absence of bile from the intestinal tract is not compatible with life. Ladd's series of 45 cases remains the largest series in the literature to date. Of these 45 cases, 15 or 33% were operable. There were five cases each of inspissated bile in a stenotic duct system, atresia of the common bile duct, and atresia of part of the hepatic duct. Five cases of partial obstruction in older children all made recoveries.

Of our 13 cases, seven were anomalies that were operable in nature. Of these the most common anomaly was that of segmental atresia of the lower portion of the common bile duct. Other operable anomalies were inspissated bile in a stenotic biliary tract, choledochal duct cyst without atresia, and a patent hepatic duct with a draining opening in its terminal portion.

Despite the operability of the anomaly, the prognosis in these cases was not good. All these patients uniformly ran stormy postoperative courses. Abdominal distention and jaundice continued to remain severe in one patient, and the intestine eviscerated at the operative site. Gastroenteritis was the cause of exitus in one patient, and another succumbed to bronchopneumonia. One died of intestinal obstruction secondary to stenosis of the ileum. Thus only two or 15% of our patients have survived.

Six cases were inoperable. Complete agenesis was present in five, and thus represents the most common anomaly in this series. The other patient had atresia of the hepatic and cystic ducts and of the gall bladder. The average duration of life in these patients was approximately five months. This is similar to Ladd's series in which the average duration of life for this class of patients was five and one-half months.

The causes of death varied. Three patients died of hepatic insufficiency. One patient, who also had an anomaly of the superior vena cava which entered the left auricle, died of bronchopneumonia. There was one operative death, and one other patient died shortly after operation of widespread hemorrhage.

BIBLIOGRAPHY

1. Stiegler, C., and Warfield, O., Clinical Proceedings of Children's Hosp. Wash., D. C., **2:** 119, Apr. 1946.
2. Nutting, R. E., and Wells, A. H.; Minnesota Med., **28:** 810, Oct. 1945.
3. Arey, L. B.: Developmental Anatomy. W. B. Saunders & Co.
4. Moolten, S. E.: N. Y. State J. Med., **43:** 727, Apr. 1943.
5. Gross, J.: Archives of Surg., **32:** 131, 1936.
6. Ladd: Annals of Surgery, **102:** 742, 1935.
7. Mitchell-Nelson: Text. of Pediatrics. W. B. Saunders & Co., 4th edition, 1946.

8. Best and Taylor: The Physiologic Basis of Medical Practice. Williams & Wilkins Co., 1939.
9. Jeghers, H.: New Eng. J. of Med., **228:** 678, 714, 1943.
10. Wintrobe: J. A. M. A., **109:** 1170, 1937.
11. Naffziger, H. C., Carr, J. L., and Foote, F. S.: Annals of Surgery, **106:** 745, 1937.
12. Sweet, L. K.: J. Pediatrics, **1:** 496, 1932.
13. Behrend, M.: Surg. Clinics of N. A., **25:** 1242, Oct. 1945.
14. Sanford, H.: Med. Clinics of N. A., January, 1946.
15. Strauss, A., Gross, J., and Kyman, S.: Annals of Surgery, **117:** 723, 1943.
16. Thompson: Edinburgh M. Journal, **27:** 523, 1892.
17. Holmes, J. B.: Am. J. Dis. Child., **11:** 405, 1916.

MENINGITIS DUE TO COMBINED MENINGOCOCCUS AND H. INFLUENZA

Case Report No. 95

Clifford J. Tichenor, M.D. J. M. 47–1872

A four year old white male was brought to the hospital because of fever, malaise, irritability and generalized petechial skin lesions. The patient was said to have been ostensible well up to forty-eight hours prior to admission when he became febrile, listless and rapidly developed confused sensorium. Other conplaints had been headache, repeated vomiting and twitching of the right arm.

The past history seemed irrelevant, nutrition, growth and development having followed a normal course. No exposure to contagion could be elicited. The family history was not remarkable.

The temperature on admission was 101° (R), the pulse rate 120 and respirations 30. The child was well developed and well nourished but appeared acutely ill. There was a diffuse scattered eruption on the trunk and extremities, appearing as dark red petechiae. There was a moderate degree of nuchal rigidity together with positive Brudzinski and Kernig signs.

Spinal puncture was performed and revealed grossly cloudy fluid, containing 7,500 white cells with 98 per cent polymorphonuclear leucocytes. The protein content was elevated to 110 mgm. per cent and the sugar was reduced to 35 mgm. per cent. Intrathecal administration of 10,000 units of penicillin diluted in 10 cc. of sterile distilled water was performed prior to bacteriological identification of the offending organism. A petechial smear showed a few pus cells and in one cell what appeared to be a gram negative diplococcus. Blood culture and nasopharyngeal culture were also obtained initially but in spite of negative cultures there seemed to be strong evidence in favor of meningococcic meningitis.

Hydration was achieved with intravenous glucose in Hartmans solution and 5 cc. of adrenal cortical extract was given intramuscularly. Penicillin was begun in the dosage of 40,000 units every three hours and concurrently sulfadiazine solution was started orally. By the second hospital day the patient was not taking fluids well by mouth so that sodium sulfadiazine was incorporated in parenteral glucose in Hartmans solution. The blood sulfadiazine level on the third day was 9 mgm. per cent.

The course seemed mild, the petechiae fading rapidly and the temperature reaching 99° (R) by lysis five days after the onset of the infection. It thus appeared that the disease was a mild meningococcic meningitis, responding satisfactorily to penicillin and sulfadiazine.

A repeat spinal puncture on the third hospital day revealed fluid containing 560 white cells with 81 per cent polymorphonuclear leucocytes, a protein level of 30 mgm. per cent and a sugar of 40 mgm. percent. The culture of the initial spinal fluid however showed gram negative bacilli—reported as Hemophilus influenza. Penicillin was therefore discontinued and 75,000 units of streptomycin diluted with 4 cc. of sterile distilled water was given intrathecally. Streptomycin in a dosage of 100,000 units was also initiated intramuscularly every three hours and the sulfadiazine was increased and given in conjunction with sodium bicarbonate by mouth.

By the fourth hospital day the spinal fluid showed only 180 white-cells with 56 percent polymorphonuclear leucocytes, 40 mgm. percent sugar and 20 mgm. percent protein. The smear revealed many pus cells with a few gram negative intracellular diplococci. All blood cultures were sterile. However there seemed to be little doubt that this patient had a double meningeal infection due to Hemophilus influenzae and Memingococcus.

The course of illness was sufficiently mild so that all antibiotics could be discontinued on the ninth day and oral sulfadiazine alone was used thereafter until the twelfth day, maintaining a blood level ranging between 6 and 11 mgm. percent. The patient was discharged as cured after 15 hospital days, having made an uneventful recovery with no evidence of any neurological sequellae.

E. COLI SEPTICEMIA

Case Report No. 96

Ralph Stiller, M.D. R. H. 46-46

R. H., a one year old colored male, was admitted Children's Hospital on January 25, 1947 with a chief complaint of vomiting and diarrhea of two days duration. The child had been hospitalized here for one week for tonsillo-pharyngitis and had been discharged as cured two days before his present admission. During the past two days he had had about four loose stools in a 24 hour period and had vomited about five times. A few hours before admission he became feverish and was brought to the hospital.

The past history revealed that the child was a premature, eight month, five pound infant born at home and hospitalized at Children's Hospital for one month. On discharge he weighed 6 pounds, 10 ounces. During the ensuing year and up to the time of the present admission the child had many attacks of upper respiratory infections as manifested by coryza, cough and pharyngitis. At the time of his present illness he could stand up in bed holding on to the side and was reported by the mother as being quite vivacious and active.

Physical examination on admission revealed a well-nourished, well-developed colored male in no particular distress with a temperature of 100 degrees. There was no evidence of dehydration and the physical examination, including examination of the chest, was negative. Admission urine was entirely negative and his blood count showed a hemoglobin of 11 grams, 5.5 million red cells with a leucocytosis of 14,000; polymorphonuclears were 52%, lymphocytes 43% and monocytes 5%. The initial diagnosis was gastro-enteritis.

During his first ten hospital days the patient ran an irregularly febrile course with temperature reaching 102 degrees. There was no vomiting but his diarrhea persisted despite feedings of boiled skimmed milk and casec. He was given sulfadiazine on an empirical basis. This was changed to penicillin 25,000 units every three hours when it became evident that the child was not improving. On his 12th hospital day he developed a temperature of 104 degrees. The fever was maintained at this level for the next four days. Sulfadiazine was re-instituted in addition to the penicillin with this new development. Suppression of breath sounds and coarse rhonchi and wheezes were noted bilaterally in both bases at this time. Blood cultures were taken on successive days. The first one was erroneously reported as Staphylococcus albus hemolyticus. Some credence was placed in this as the same organism had been isolated from three

consecutive stool cultures. On the basis of this report the sulfadiazine was maintained at 1½ grains per pound of body weight per day and the penicillin dosage was increased to 100,000 units every three hours. Two days later the second culture was reported as showing innumerable colonies of E coli. On re-examination, the first culture was seen to be similar and it was

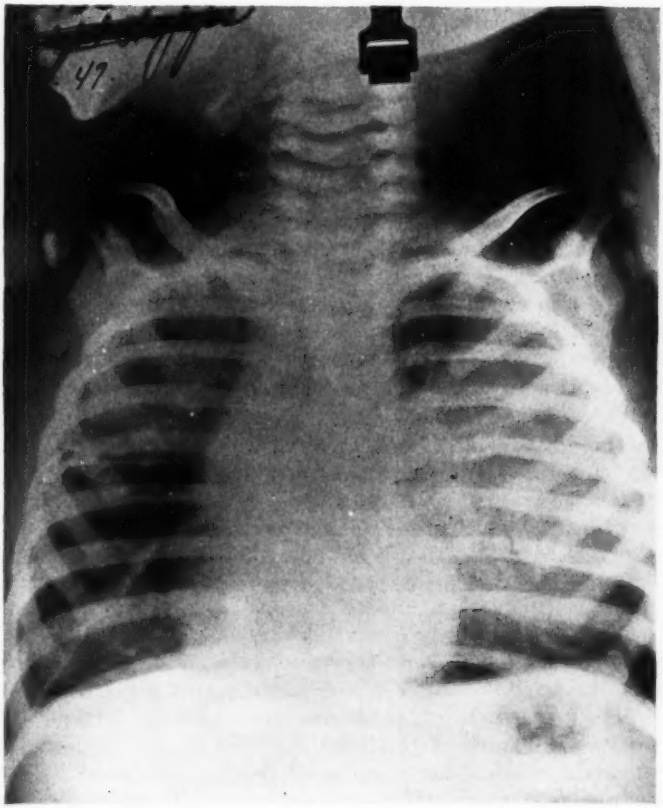

FIG. 1

considered that streptomycin was indicated. The child was given 2 million units in the first 24 hours and thereafter 1 million units a day until discontinued. 25,000 units were given every three hours by mouth, 100,000 units every three hours intramuscularly after an initial 200,000 units was given intravenously. Penicillin was discontinued at this time.

After a week had elapsed on streptomycin and sulfadiazine an evaluation of the child showed a weak, irritable infant, unable to sit up or even hold up his head. He had a poor appetite, a continuing fever of from 100 degrees to 102 degrees and persistent signs of respiratory distress with rapid breathing, basilar rhonchi and diminished breath sounds bilaterally at both bases. On the credit side his diarrhea had stopped dramatically, his blood cultures were consistently sterile and the spinal fluid was negative. His urines had consistently shown some albuminuria. The red cell count was well maintained with frequent transfusions of blood. With the cessation of the diarrhea the oral dosage of streptomycin was stopped and shortly after that all medication was discontinued. He was removed from the quarantine that had been imposed on the diarrhea ward in which he had been placed and for the first time, on his 26th hospital day, it was possible to get an adequate chest x-ray. This showed some shift of the heart and mediastinum to the right with a triangular opacity in the region of the right cardiophrenic angle, interpreted as an area of atalectasis. Diffuse infiltration throughout the left chest was consistent with bronchopneumonia. With cessation of therapy the child's temperature rose promptly to 103 degrees. A combination of sulfathiazole and sulfadiazine was started to a total dosage of 3 grains per pound of body weight per day. On this therapy and with a stormy respiratory course the child gradually improved over a three and one half week period. Chest signs gradually abated, he began to eat, gain weight and regained his strength. At the time of discharge after a seven week hospital course he still had some residual x-ray signs in his chest and was still quite weak. However, it was felt that the care he would get at home with follow-ups in the clinic would be adequate for his eventual complete recovery.

COMMENT

Streptomycin is considered the drug of choice in the treatment of gram negative bacillus infections. E. coli is particularly sensitive to Streptomycin in vitro and therefore the drug seemed indicated in this patient. The dramatic clearing of the blood stream with the administration of streptomycin was probably aided by the decision to give a massive intravenous dose producing a high blood level, coupled with large intramuscular doses for the first 24 hours of treatment. We have had moderately good results in the treatment of some cases of diarrhea in this hospital using oral streptomycin and knowledge of this prompted the use of the drug orally in this patient. Colony counts have shown an almost uniform decrease in the number of coliform organisms in the stool when streptomycin is taken by mouth, even when there is no beneficial effect on the diarrhea. Since at the time this septicemia occurred the child had a moderately

severe diarrhea it was felt that the colon bacillus had probably invaded the blood stream from the intestine and thus any medication aimed at reducing the invasiveness of the organism would be beneficial. As a result of this mode of therapy the child's diarrhea stopped within a day or two of streptomycin administration. Many workers feel that since resistance to streptomycin is rapidly built up by the organism massive doses should be given for a few days rather than small doses over a long period of time. In this case massive therapy was used and maintained possibly longer than was absolutely necessary.

With the remission of the septicemia and yet the maintenance of the febrile course, and particularly with the upward course of temperature on stopping medication it became obvious that some other focus was present. It is impossible to say exactly where the pulmonary infection fits into the picture since some signs of chest pathology were discernible before the septicemia became manifest. Suffice it to say that it acted in every way like a non-specific broncho-pneumonia that was slow to resolve. Its slow but steady response to sulfonamide therapy speaks against a virus etiology. It might have been due to E. coli but there is no way of proving this or for that matter of disproving it. The combination of sulfathiazole and sulfadiazine was used not because of any specific therapeutic effect inherent in the sulfathiazole but to take advantage of the fact that a high therapeutic level can be obtained with a minimum of kidney damage when both drugs are used. Even with this precaution large amounts of albumin were spilled in the urine during the period of high sulfonamide dosage. Whether this was due to the drugs or was more a febrile albuminuria due to the disease process is again a moot point. Conclusions cannot be drawn from one case but the use of streptomycin in large dosage is presented for consideration in cases of E. coli (and other gram negative bacilli) septicemia. The use of streptomycin empirically in intractable diarrheas is worth a trial.